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OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: ***1,4-Bis(bromoacetoxy)-2-butene*** : Risk Characterization for the Reregistration Eligibility Decision (RED) Document.
PC Code: 035605 **DP Bar Code:** D251936

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Attached is RASSB's Risk Characterization of 1,4-Bis(bromoacetoxy)-2-butene **(BBAB)** for purposes of issuing a Reregistration Eligibility Decision (RED) document for this chemical. The Section Number suggested in the heading and subtitle (five) is an arbitrary number. The real number and appropriate format will be determined when the document is integrated with other parts of the RED document.

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5.0 BACKGROUND

The chemical 1,4-Bis(bromoacetoxy)-2-butene (**BBAB**) is registered for use in (1) control of slime formation in oil field injection water and other field water systems; (2) control of bacterial and/or fungal slime in pulp and paper mills in paper manufacturing processes; and (3) the preservation of water-based coatings. Using **BBAB** in pulp and paper mills as a slimicide in paper machines or in the preservation of paper coating formulations/chemicals is considered an indirect food use. The Food and Drug Administration (FDA) has approved this use under 21 CFR 176.300, Slimicides. However, regulation of **BBAB** under Section 409 of the Federal Food, Drug, and Cosmetic Act (FFDCA) does not relieve the registrant of meeting the standard under Section 408 as amended by the Food Quality Protection Act (FQPA), when the active ingredient is subject to regulation as a food-use pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Under Section 408, a determination of safety for residues of a pesticide that may be in food is required, and as defined in Section 408(b)(2)(ii),"that there is a reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residues, including all anticipated dietary exposures and all other exposures for which there is reliable information." Therefore, a dietary risk assessment under FQPA is necessary for **BBAB** to support the intended use in food-contact paper and paperboard.

To complete a risk assessment for an indirect food use chemical for which the FDA has established a food additive regulation that specifically states that the use is "safe", the Antimicrobials Division, OPP, established a two-tiered system for toxicology testing requirements. Tier I toxicology data requirements would apply to all indirect food additives that result in residue concentrations ranging from 0-200ppb. The requirements would consist of an acute toxicity testing battery, subchronic toxicity studies in both the rodent and non-rodent (with the inclusion of neurotoxicity testing endpoints in the rodent assay), a developmental toxicity study in the rat, a two-generation reproduction toxicity study in the rat, and a mutagenicity testing battery. The registrant may choose to combine the developmental and reproductive toxicity testing per FDA protocols, but if so, must first submit the protocol to the Agency for approval. Tier II studies would be triggered by the presence of significant (i.e. $200ppb) residues in food or evidence of significant toxicity from the Tier I data set, which may include developmental / reproductive, or other systemic toxicity such as presence of neoplastic growth or significant target organ toxicity. In such cases, chronic toxicity and carcinogenicity testing would be required.

The purpose of risk characterization is to quantify the potential health risks associated with exposure to the registered uses of **BBAB**. Based on the discussions in **Section X** (Exposure Assessment) and **Section Y** (Toxicity Assessment), the total daily exposure and Margin of Exposure (**MOE**) for each potential exposure receptor and potential exposure routes are calculated. The uncertainty associated with each of the risk assessment procedures is also discussed in this section. However, the toxicology database submitted by the registrant *is inadequate for the purpose of conducting a dietary risk assessment.* Therefore, a final risk assessment must be deferred, pending submission of the missing studies.

5.0 EXECUTIVE SUMMARY

In order to issue a Reregistration Eligibility Decision (RED) Document for 1,4-Bis(bromo-acetoxy)- 2-butene **(BBAB)**, a risk assessment (RA) has been performed to evaluate potential human risks that may result from exposure to this chemical. **BBAB** is used for controlling microbial growth in pulp and paper mills, secondary oil recovery injection water, and as a preservative in water-based coatings. In the risk assessment associated with human health concerns, different potential exposure receptors are identified for these registered uses of BBAB. These receptors are:

- For BBAB used in oil field injection water, only the **Occupational Primary Handler** who is mixing and loading the chemical into the system is considered as the primary potential exposure receptor;

- For BBAB used in water-based coatings, both the **Occupational Primary Handler** who is mixing and loading the chemical into the system and the **Occupational Secondary Handler/ Residential Handler** who actually applies the BBAB-containing coating to paint indoor or outdoor appliances is considered as the primary potential exposure receptors; and

- For BBAB used in pulp and paper mills, the **Occupational Primary Handler** who is mixing and loading the chemical into the system is considered as the primary potential exposure receptor; along with **Residential Receptors** who ingest food containing **BBAB** residue from **BBAB**-treated food contact papers.

Because of an insufficient toxicology database, the following risk assessments must be deferred, pending submission of additional toxicology data:

- The complete dietary risk assessment for **Residential Receptors** who ingest food containing **BBAB** residue from BBAB-treated food contact papers; and

- The inhalation risk assessments for **Occupational Secondary Handler /Residential Handlers** who actually apply the BBAB-containing coating to paint indoor or outdoor appliances.

In risk calculations, the results of the primary occupational handler assessment for short-, intermediate-, and long-term handler scenarios indicate that dermal MOEs are acceptable (e.g., MOEs >300) for mixing/loading liquids for general pulp and paper and oil well injection fluids.

For primary occupational handler, the following scenarios bear unacceptable risks:

- Primary occupational handler who is mixing/loading liquids for general preservative use, and
- Primary occupational handler who is mixing/loading liquids for paint manufacturing.

The dermal risks associated with both the **Occupational Secondary Handler** and **Residential Handler** who actually apply the **BBAB**-containing coating to paint indoor or outdoor appliances are unacceptable. For

Secondary Handler, the **unacceptable** application scenarios include:

- loading/applying paint with a paint brush,
- loading/ applying paint with an airless sprayer, and
- loading/applying paint with an aerosol can.

Based on the reviews of the toxicology data for **BBAB**, The Antimicrobials Division, Office of Pesticide Programs, has determined that BBAB used in Oil Field Injection Water will not pose unreasonable risks or adverse effects to human.

The determinations of Margins of Exposure for non-food use of **BBAB** as general preservative and as preservative in water-based coatings were based upon the use of very conservative assumptions regarding the toxicological hazard of BBAB, and the use of exposure models rather than actual exposure data. The Antimicrobials Division, Office of Pesticide Programs, believes that with the submission of additional hazard and exposure data, the risk assessment for the uses of BBAB as general preservative can be refined . The additional toxicology data required consist of a dermal penetration and/or 90-day dermal toxicity study in the rat, a 28-day inhalation toxicity study in the rat, and a neurotoxiciy screening battery. The additional exposure information required is the complete **BBAB** use-profile.

Similarly, dietary risk assessment from the use of **BBAB** for control of bacterial and/or fungal slime in pulp and paper mills in the manufacture of food-contact paper is deferred at this time, based upon the lack of an adequate hazard database to assess risk from the indirect food use of BBAB, and migration data that are considered unacceptable. The additional hazard data required will depend upon the calculated residues of **BBAB** expected in food. If residues are calculated between 0-200 ppb, then, in addition to the existing hazard database and per the Antimicrobials Division's policy, a 90-day toxicity study in the non-rodent and a 2-generation reproduction toxicity study will be required. If residues in food exceed 200 ppb, then in addition to the existing hazard data and the two additional studies just mentioned, a developmental toxicity study in the rabbit, a chronic toxicity study in the non-rodent, and carcinogenicity studies in the rat and mouse will be required.

5.2 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

The chemical of concern, 1,4-Bis(bromoacetoxy)-2-butene (**BBAB**), is a dark brown opaque and slightly viscous liquid. The vapor pressure of **BBAB** is very low, 1.59×10^{-6} at 20°C, and the chemical is not very volatile. **BBAB** is stable under acidic conditions. At higher pH (pH >5), **BBAB** is hydrolyzed into different hydrolytic products, including bromoacetic acid (BA), 1-bromoacetoxy-4-hydroxy-2-butene (BHB) and 1-bromoacetoxy-4-acetoxy-2-butene (BAB). BA was the major hydrolytic product. All of these products tend to degrade further.

5.3 HAZARD ASSESSMENT

5.3.1 Hazard Profile

As summarized in **Table 5-1**, eight studies have been submitted by the registrant to characterize the toxicity of **BBAB**. **BBAB** is moderately toxic in acute oral and dermal studies. The acute toxicity data on **BBAB** technical is summarized in **Table 5-2.** There are no available acute inhalation, primary eye irritation, primary skin irritation or dermal sensitization studies. Due to the corrosive properties of **BBAB**, this chemical has been assigned Toxicity Category I classification for acute inhalation toxicity, eye irritation, dermal irritation and dermal sensitization.

As indicated by the subchronic rat study (MRID 44757001), the primary target organ for oral exposure to **BBAB** is the stomach. In both sexes, at the low-treatment dose (4.5mg/kg/day), slightly increased incidence of minimal hyperkeratosis and hyperplasia of the nonglandular mucosa of the stomach were noticed. Mid- and high-dose animals had mild anemia (possibly due to blood loss from the stomach).

Two studies were submitted to evaluate the developmental toxicity of **BBAB,** one range-finding study (MRID 4479401) and one definitive rat prenatal developmental toxicity study (MRID 44750901). Results of these two studies indicate there was no evidence of developmental toxicity for **BBAB**, but the data are insufficient to make a full assessment. There is no study to evaluate the reproductive toxicity of **BBAB** which is required for indirect food uses of this chemical.

Signs of neurotoxicity were observed in the subchronic toxicity study (MRID 44757001) and the range finding developmental study (MRID 44749401) study, including: hypoactivity; head held low; drooping/closed eyelid; body dragging, rocking, lurching or swaying while walking; flattened body/extended limbs; prostration; circling; splayed hindlimbs; walking on tiptoes; sporadic nasal clicks; and hunched or unkempt appearance. In addition, in the acute dermal study (MRID 43152401), congested meningeal vessels were observed during necropsy. No neurotoxicity tests were submitted to characterize these observations further.

Three mutagenicity studies were submitted to evaluate the mutagenic potential of **BBAB**. Although **BBAB** is mutagenic in the mouse lymphoma assay under conditions of S-9 activation (MRID 43202601), **BBAB** is negative in both the Ames test either with or without S-9 activation (MRID 43201001) and in the *in vivo* ICR mouse bone marrow micronucleus test (MRID 43156301). There are no available carcinogenicity data to evaluate the potential carcinogenic effects of **BBAB**.

Table 5-2: Acute Toxicity of 1,4 (bis) Bromoacetoxy-2-butene (BBAB)

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	431811-01	LD_{50} = 292 mg/kg (**%**), 163 mg/kg (**&**), and 220mg/kg (combined)	II
81-2	Acute Dermal	431524-01	LD_{50} > 2000mg/kg	III
81-3	(1) Acute Inhalation	No Study available		I
81-4	(1) Primary Eye Irritation	No Study available		I
81-5	(1) Primary Skin Irritation	No Study available		I
81-6	(1) Dermal Sensitization	No Study available		I

Note:

(1). Acute inhalation, primary eye irritation, primary skin irritation and dermal sensitization studies were not available due to the corrosive properties of **BBAB**. For these endpoints, **BBAB** was classified as toxicity category I on the basis of its known corrosivity.

For non-food uses of **BBAB**, the following toxicology studies were identified as data gaps:

1. A dermal penetration study (OPP Guideline 85-7, OPPTS Number 870-7600) or
   A 90-day dermal study (OPP Guideline 82-3, OPPTS Number 870-3250),
2. A 28-day inhalation study at one dose level (with 2.5% **BBAB**) (OPP Guideline 82-4, OPPTS Number 870-3465), and
3. An oral neurotoxicity screening battery study (OPP Guideline 81-8, OPPTS Number 870-6200).

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Because use of **BBAB** in pulp and paper mills as a slimicide in the paper making or in the preservation of paper coating formulations/chemicals is considered an indirect food use, and as discussed in the **Background Section**, the following toxicity data would be necessary depending on the level of anticipated residue:

If **BBAB** residue in food is found to be greater than 200 ppb, five additional studies would be required:

1. A developmental toxicity study in the rabbit (OPP Guideline 83-3, OPPTS Number 870-3700),
2. A two-generation reproductive toxicity study in the rat (OPP Guideline 83-4, OPPTS Number 870-3800),
3. A chronic study in non-rodents (OPP Guideline 83-1, OPPTS Number 870-4100),
4. A combined chronic toxicity/carcinogenicity study in the rat (OPP Guideline 83-5, OPPTS Number 870-4300), and
5. A carcinogenicity study in the mouse (OPP Guideline 83-2, OPPTS Number 870-4200).

If the registrant provides data that show **BBAB** residue in food is between 0-200 ppb, only two additional studies are required:

1. A 90-day non-rodent study with the inclusion of neurotoxicity testing endpoints (OPP Guideline 82-1, OPPTS Number 870-3100); and
2. A two-generation reproductive toxicity study in the rat (OPP Guideline 83-4, OPPTS Number 870-3800).

5.3.2 FQPA Considerations

Consideration of the risks posed to potentially susceptible subpopulations, including females of child-bearing age as well as infants and children, as mandated by the Food Protection Act, must be deferred at this time. Although the single developmental toxicity study available for **BBAB** showed no evidence of susceptible subpopulations, with the submission of the additional hazard data, an appropriate risk assessment can be conducted for these populations.

5.3.3 Dose Response Assessment

The toxicological endpoints selected, and rationale for selection, are summarized in **Table 5-3**. Because there are data gaps, a final dietary risk assessment for **BBAB** must be deferred , pending submission of the missing data. The endpoints selected for dietary exposure are for interim risk assessment only. There is no appropriate dermal absorption study for **BBAB** available. Because of the corrosivity of this chemical, 100% dermal absorption should be used in dermal risk assessment. Because there is no appropriate dermal toxicity study available, an oral toxicity endpoint is selected to be use in dermal risk assessments per OPP policy.

Table 5-3. Summary of Toxicological Dose and Endpoints for BBAB for Use in Human Risk Assessment [(1)]

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Short-Term, Intermediate-Term, and Long Term (Dermal)	LOAEL [(3)] = 4.5 MOE = 300	Based on microscopic findings of hyperkeratosis and hyperplasia of the non-glandular mucosa of the stomach in both sexes and edema of the stomach in the female.	90-day Rat Gavage study MRID 44757001

Note:

(1). LOAEL = lowest observed adverse effect level, MOE = margin of exposure

(2). The toxicological endpoints for dietary and inhalation risk assessment for **BBAB** must be deferred , pending submission of the missing studies.

(3). The use of a 100% dermal absorption rate is required for dermal risk assessments.

5.4 EXPOSURE ASSESSMENT

5.4.1 Summary of Registered Uses

The chemical 1,4-Bis(bromoacetoxy)-2-butene (**BBAB**) was registered to be used (1) for control of slime formation in oil field injection water and other field water systems; (2) for control of bacterial and/or fungal slime in pulp and paper mills in paper manufacturing processes; and (3) for the preservation of water-based coatings. According to information provided by the registrant, all **BBAB** produced is currently used as a slimicide in the paper making process or in the preservation of paper coating formulations/chemicals. It is anticipated that most (approximately 80%) of the future production of **BBAB** will be in the pulp and paper making industry (Drake, 1998). The potential exposure scenarios for all these registered uses of **BBAB** are summarized in this section. The estimated daily exposed dose for each of these exposure scenarios is summarized in **Tables 5 -4**, **5-5**, and **5-6**.

5.4.2 Dietary Exposure

5.4.2.1 Food Exposure

BBAB is used as a slimicide in the manufacture of paper and paperboard products that contact food. This use results in a potential dietary exposure of this chemical to humans. The registrant submitted a migration study for this chemical to the Food and Drug Administration in the 1960's. This migration study does not reflect the use of simulating solvents that are recommended in the present FDA Guidelines. Consequently, the Agency has used a worst case calculation for estimating the level of **BBAB** that may migrate from **BBAB**-treated paper into food through contact with the treated paper. The estimated maximum concentration of **BBAB** residue in contacted food would be 0.600 ppm or 600 ppb.

5.4.2.2 Water Exposure

In general, it is believed that **BBAB** will not a cause dietary drinking water concern. **BBAB** was registered to be used (1) for control of slime formation in oil field injection water and other field water systems; (2) for control of bacterial and/or fungal slime in pulp and paper mills in paper manufacturing processes; and (3) for the preservation of water-based coatings.

The Agency considers the enhanced oil recovery use to generally be an environmentally contained system. The water for this type of use is injected into closed geological formations. Additionally, the application rate for **BBAB** will be 5.5 ounces of Busan 1210 (an 80% active product) per each 1000 barrels of water. The residence time of water injected into the ground is at least several days. In those cases where the enhanced oil recovery is not a closed system, the user must obtain a National Pollution Discharge Elimination System (NPDES) permit before discharging water from the oil recovery system into public waterways. The NPDES permit requires that the recovery water be filtered and cleaned to remove the oil-related contaminants prior to discharge. This will also likely remove a portion of the 1 ppm **BBAB** from the water.

The use of **BBAB** in pulp and paper making allows the use of up to 0.30 pounds of **BBAB** per ton of paper. The waste water from pulp and paper making is discharged into holding ponds or lagoons. The typical measurements for such lagoons are approximately one-forth mile wide and one-half mile long. Applications of **BBAB** in pulp and paper mills are generally intermittent, consisting of maximum cycles of 12 hours on followed by 12 hours off. The pH in lagoon water is typically 7 or higher. The label use rate for **BBAB** is 3 ppm in the water. Therefore, the pulse dosing results in a potential discharge concentration of 1.5 ppm in the influent to discharge systems(This is based on the 12 hour treatment cycles resulting in a 50% dilution).

BBAB can be degraded by both hydrolysis and by biodegradation. The **BBAB** hydrolysis rate is pH dependent. At pH 7, the hydrolytic half-life of **BBAB** is 6.9 hours and at pH 9 the half-life of **BBAB** is 4 minutes. At the higher pH levels expected to be found in the paper mill discharge, the **BBAB** half-life is expected to be less than 7 hours in the lagoon water. The discharge waters from paper mills typically are retained in the lagoons for several days. The biodegradation rate of **BBAB** in paper mill discharge water was calculated using a BIODEG model developed in collaboration with the USEPA. Using this model and assuming biodegradation would be the only route of degradation, the concentration of **BBAB** in discharge water in lagoons would be 0 ppb after 1 day in the lagoon. Through a combination of hydrolysis and biodegradation, **BBAB** would be expected to be degraded in much less than 1-3 days after discharge into an aerated stabilization basin(lagoon).

Therefore, it is concluded that there will be little potential that **BBAB** use will contaminate drinking water sources.

5.4.3 Occupational Exposure

Based on the registered uses of **BBAB**, two levels of potential occupational handler exposures were identified in the exposure assessment:

- **Primary handlers** -- persons in a manufacturing setting who are handling **BBAB** pesticide products for use as a slimicide in paper machines, in the preservation of papermaking coating formulations/chemicals, in oil field injection systems, in pulp and paper mills, and as a preservative in slurries, emulsions, and water-base coatings, such as paints.

- **Secondary handlers** -- persons in a residential or commercial setting who are handling paint products to which **BBAB** has been added.

5.4.3.1 Primary Handler Exposure

Based on the registered uses of **BBAB** , the primary handler exposure scenarios can be classified into two groups: **non-paint related scenarios** and **paint related scenarios**:

Non-Paint Scenarios

- mixing/loading liquids for oil well injection fluid,
- mixing/loading liquids for general preservative use, and
- mixing/loading liquids for pulp and paper mills.

Paint Scenario

- mixing/loading liquids for paint manufacturing
- mixing/loading liquids for general preservative use

(NOTE: Data are not available to evaluate the scenario: loading/applying paint with a paint roller.)

5.4.3.2 Secondary Handler Exposure

Three major paint exposure scenarios for **secondary occupational handlers (professional painters)** are identified for occupational postapplication use:

- loading/applying the paint using a paint brush,
- loading/applying the paint with an airless sprayer, and
- applying paint with an aerosol can.

5.4.4 Residential Exposure

Only uses of **BBAB** treated water-base paint are identified as potential non-food secondary residential exposure scenarios. Based on the potential for paint use patterns, EPA has identified four major exposure scenarios for **secondary residential handlers** of paint including:

- loading/applying the paint using a paint brush,
- loading/applying the paint with an airless sprayer, and
- applying paint with an aerosol can.

The scenarios are similar to the occupational secondary handlers, except that the residential handlers are expected to handle less of the product per day.

5.5 RISK AGGREGATION AND RISK CHARACTERIZATION

An aggregate exposure and risk assessment was not performed for **BBAB** at this time, based upon the limited use patterns for the chemical and the nature of the exposures. It is not expected that from current uses of **BBAB** that there will be concomitant exposures to this chemical that warrant an aggregate exposure and risk assessment. Non-food uses of **BBAB** involve uses as a paint additive and there are no other expected residential exposures other than through use in paint. There are also no concerns for the presence of **BBAB** in drinking water supplies based upon the known environmental fate of the compound. Therefore, the indirect food applications of **BBAB** as well as the residential uses of **BBAB** can be assessed for risk separately at this time.

Based on the discussions in the hazard assessment and exposure assessment, the total daily exposure and Margin of Exposure (**MOE**) for each potential exposure receptor and potential exposure routes for which there are sufficient

data are calculated. The risk characterizations of exposure assessment for **BBAB** are summarized in **Tables 5-4**, **5-5**, and **5-6**. In general, if the **MOE** is greater than the specified Accepted MOE, the risk is considered acceptable. Otherwise, when the **MOE** is less than the specified safety factor, exposure to the specific chemical through the potential exposure routes is considered to pose a health concern.

5.5.1 NON-DIETARY EXPOSURE

5.5.1.1 Primary Occupational Handler

The risk characterizations associated with the primary occupational handler are summarized in **Table 5-4** The assessment for short-, intermediate-, and long-term handler scenarios indicates that the dermal exposure route is the primary exposure route of concern. The calculated dermal **MOE**s are acceptable (e.g., **MOE**s >300) for mixing/loading liquids for general pulp and paper, and oil well injection fluids. The risks associate with dermal exposure to paints are acceptable as long as enclosed manufacturing systems are in place (e.g., mechanical pump systems).

When **BBAB** used as a general preservative, it bears an unacceptable risk to primary occupational handlers mixing and loading the **BBAB** liquids (calculated MOE =38, acceptable MOE = 300). However, this calculation is based on the assumption that the process is occurring in an open system. If the registrant could prove that general preservatives are pumped using a closed system then that would most likely eliminate this pathway from consideration.

Based on the same consideration, if liquids are poured in an open system, it bears an unacceptable risk to primary occupational handlers mixing and loading **BBAB** liquid for paint manufacturing (calculated MOE =64, acceptable MOE = 300). Note that inhalation exposure is negligible because of a low vapor pressure (10^{-6}) in the pulp/paper, oil, general preservative, and paint industries unless mists or sprays are expected to be generated.

5.5.1.2 Secondary Occupational Handler

The results of the secondary occupational handler (professional painters) assessment (**Table 5-5**) indicate that **MOE**s are unacceptable for both inhalation and dermal exposure routes for all following scenarios:

- Loading/applying paint with a paint brush;
- Loading/applying paint with an airless sprayer; and
- Loading/applying paint with an aerosol can.

The calculation is based on the assumption that paint contains the label recommended maximum 2.5 percent active ingredient.

Table 5-4: Risk Characterization of Exposure Assessment to Primary Occupational Handlers

Scenario	Route of Exposure	Estimated Daily Dose (mg/kg/day)	Selected Toxicity End Point (mg/kg/day)	MOE	
				Acceptable MOE	Calculated MOE[a]
NON-PAINT					
Mixing/loading liquids for oil well injection - Open-pour liquids	Oral			-	-
	Inhalation			-	-
	Dermal	0.001	4.5 (LOAEL)	300	4,500
Mixing/loading liquids for oil well injection - Pump liquids	Oral			-	-
	Inhalation			-	-
	Dermal	0.000054	4.5 (LOAEL)	300	83,000
Mixing/loading liquids for general preservative use - Open-pour liquids	Oral			-	-
	Inhalation			-	-
	Dermal	0.12	4.5 (LOAEL)	300	38
Mixing/loading liquids for general preservative use - Pump liquids	Oral			-	
	Inhalation			-	
	Dermal	0.0062	4.5 (LOAEL)	300	730
Mixing/loading for pulp and paper mills - Pump liquids	Oral			-	
	Inhalation			-	
	Dermal	0.0013	4.5 (LOAEL)	300	3,500
PAINT					
Mixing/loading liquids for paint manufacturing - Open-pour liquids	Oral			-	
	Inhalation			-	
	Dermal	0.07[b]	4.5 (LOAEL)	300	64[b]
Mixing/loading liquids for paint manufacturing - Pump liquids	Oral			-	
	Inhalation			-	
	Dermal	0.0038[b]	4.5 (LOAEL)	300	1,200[b]

Note: (a). The exposure scenarios with the calculated MOE in shaded cells pose an unacceptable hazard concern.
(b). Based on 1,000 gallons of paint manufactured per day in an open system.

Table 5-5: Risk Characterization of Exposure Assessment to Secondary Occupational Handlers Loading/Applying Paint at Baseline

Scenario	Route of Exposure	Estimated Daily Dose (mg/kg/day)	Selected Toxicity End Point (mg/kg/day)	MOE	
				Accepted MOE	Calculated MOE[a]
Occupational Handlers					
Loading/applying paint with a paint brush	Oral	-		-	-
	Inhalation	3.9	Pending[b]	NA[b]	Pending[b]
	Dermal	3.9	4.5 (LOAEL)	300	1.2
Loading/applying paint with a roller[c]	Oral	-		-	-
	Inhalation	NA	Pending[b]	NA[b]	NA[b]
	Dermal	NA	4.5 (LOAEL)	300	NA
Loading applying with an airless sprayer	Oral	-		-	-
	Inhalation	8.6	Pending[b]	NA[b]	Pending[b]
	Dermal	8.4	4.5 (LOAEL)	300	0.5
Loading/applying with an aerosol can	Oral	-		-	-
	Inhalation	0.22	Pending[b]	NA[b]	Pending[b]
	Dermal	0.22	4.5 (LOAEL)	300	21

Note:

(a). The exposure scenarios with the calculated MOE in shaded cells pose an unacceptable hazard concern.

(b). Because of an insufficient database, the inhalation risk assessments for **Occupational Secondary Handler** who actually apply the **BBAB**-containing coating to paint indoor or outdoor appliances must be deferred, pending submission of the missing studies:

(c). No information for applying paint with a roller is available

Table 5-6: Risk Characterization of Exposure Assessment to Secondary Residential Handlers Loading/Applying Paint at Baseline

Scenario	Route of Exposure	Estimated Daily Dose (mg/kg/day)	Selected Toxicity EndPoint (mg/kg/day)	MOE	
				Accepted MOE	Calculated MOE[a]
Residential Handlers					
Loading/applying paint with a paint brush	Oral	-		-	-
	Inhalation	1.9	Pending[b]	NA[b]	Pending[b]
	Dermal	1.9	4.5 (LOAEL)	300	2.4
Loading/applying paint with a roller[C]	Oral	-		-	-
	Inhalation	NA	Pending[b]	Pending[b]	NA
	Dermal	NA	4.5 (LOAEL)	300	NA
Loading/applying with an airless sprayer	Oral	-		-	-
	Inhalation	5.1	Pending[b]	NA[b]	Pending[b]
	Dermal	5.0	4.5 (LOAEL)	300	0.9
Loading/applying with an aerosol can	Oral	-		-	-
	Inhalation	0.26	Pending[b]	NA[b]	Pending[b]
	Dermal	0.26	4.5 (LOAEL)	300	17

Note: (a). The exposure scenarios with the calculated MOE in shaded cells pose an unacceptable hazard concern.

(b). Because of an insufficient database, the inhalation risk assessments for **Residential Handlers** who actually apply the **BBAB**-containing coating to paint indoor or outdoor appliances must be deferred, pending submission of the missing studies:

(c). No information for applying paint with a roller is available

5.5.1.3 Residential Handler

The results of the residential handler assessment (**Table 5-6**) indicate that **MOE**s are unacceptable for both inhalation and dermal exposure routes for all following scenarios:

- Loading/applying paint with a paint brush;
- Loading/applying paint with an airless sprayer; and
- Loading/applying paint with an aerosol can.

The calculation is based on the assumption that paint contains the label recommended maximum of 2.5 percent active ingredient. Because no estimated inhalation information when applying paint with a roller is available, the estimated daily dose for applying with a paint brush is used in the calculation. Evaluation of inhalation exposure includes an evaluation of the potential dermal exposure. Therefore, an aggregate exposure risk assessment for both dermal and inhalation exposure routes is not required

5.5.2 Dietary Exposure

Because the toxicology database is insufficient, the dietary risk assessment for Residential Receptors who ingest food containing **BBAB** residue from **BBAB**-treated food contact papers must be deferred, pending submission of the missing studies.

5.6 UNCERTAINTY ANALYSIS

There are uncertainties involved in each risk assessment process. In order to minimize the uncertainties, some data gaps are identified and discussed in this section.

5.6.1 Uncertainties and Deficiencies in Risk Assessment

In order to minimize the associated uncertainties in the non-food and indirect food risk assessments**, Table 5-7** summarizes the data gaps considered as required data for each exposure scenario.

5.6.1.1 Route to Route Extrapolation

There is no inhalation toxicological study available. As discussed in the hazard assessment, route to route exposure for inhalation risk assessment is not appropriate for this risk assessment. The route to route exposure should only be used when the following conditions are met:

1. The considered effects are independent of the exposure route;
2. Absorption efficiency is the same among routes or differs by a known degree;
3. Half-life of the substance is long (exhibiting stable blood and/or tissue concentration);
4. First pass effects by the routes of concern are minimal;
5. There is no significant chemical transformation by intestinal flora; and
6. The chemical is relatively soluble in body fluid.

For, **BBAB**, the route to route extrapolation is not considered to be appropriate because:

1. There is no pharmacokinetic information available to determine the absorption efficiency, biological-half life and the biological distribution of the chemical in the system; and
2. The chemical is corrosive and first pass effects by route should not be considered to be minimal.

Therefore, **a 28-day inhalation study** is considered as a data gap and is required to evaluate the risk associated with inhalation exposure.

5.6.1.2 Route to Route Extrapolation (Form Oral to Dermal)

As discussed in **Section 5.6.1.1**, the same conditions should be met for route to route extrapolation from oral to dermal exposure. In evaluating the exposure of **BBAB** through the dermal exposure route, The **LOAEL** is 4.5 mg/kg/day in the 90-day subchronic rat study is used as a toxic endpoint. There is no **NOAEL** identified in this study. The dermal exposure route is considered as the most important exposure route for occupational receptors. Therefore, a **90-day dermal study** is identified as a data gap. It is required to minimize the uncertainties caused by route to route extrapolation from oral to dermal risk assessment.

5.6.1.3 Dermal Absorption

In evaluating the exposure of **BBAB** through the dermal exposure route, 100% dermal absorption is used in the dermal risk assessment. This conservative assumption may overestimate the risk through the dermal exposure route. Therefore, **a dermal absorption study** is identified as a data gap and is required to minimize the uncertainties caused by assuming 100% dermal absorption in this risk assessment

5.6.1.4 Neurotoxic, Reproductive and Carcinogenic Effects

There are no submitted neurotoxicity studies. However, signs of neurotoxicity were noted in the subchronic study, range-finding prenatal developmental study, and acute dermal study. Therefore, acute and subchronic neurotoxicity testing is required in order to adequately characterize the neurotoxic potential of **BBAB**. In addition, there are no available data to assess reproductive toxicity or carcinogenicity of **BBAB**. Depending upon the calculated residue of **BBAB** from use as an indirect food additive, one or both of these studies will be required.

5.6.1.5 Dietary Risk

Comparison of the available toxicology data for **BBAB** with the requirements as discussed above for an indirect food use shows that there are several data gaps for adequate assessment of dietary risk. For example, in the interim dietary exposure assessment, the Agency used the FDA modeling methodology to calculate the residue. The residue using this methodology was calculated to be 600 ppb in food. The modeling scheme assumes that 100% of the **BBAB** paper additive migrates to food. This is likely an overestimate of the true level of residue in food, but there are no other currently available exposure data with which to perform an assessment of dietary risk. The Agency

cannot at this time perform an adequate dietary risk assessment based on the lack of adequate exposure data and the lack of an adequate toxicology data.

5.6.2 Uncertainties and Deficiencies in Exposure Assessment

5.6.2.1 No Complete Use -Profile

A use-profile has not been completed for **BBAB**. In the absence of the profile, information from **BBAB** labels (e.g., EPA Reg 1448-353 and 1448-374) has been used to identify probable use scenarios for **BBAB**. These may have to be adjusted when the **BBAB** use-profile is completed.

At this time, **BBAB** chemical specific handler or post-application exposure studies that meet Agency guidelines have not been identified. Surrogate dermal and inhalation data from the Pesticide Handlers Exposure Database (PHED) Version 1.1,Chemical Manufacturers Association (CMA) database, and draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments were used to assess handler exposure. Data for the following scenario were not available:

- loading/applying paint with a paint roller.

In addition, it should be note that CMA surrogate data have the following deficiencies:

- The inhalation concentrations were typically below the detection limits, so the unit exposures for the inhalation exposure route could not be accurately calculated.
- The quality of the CMA data were assessed using the same grading criteria as PHED and the grades were all at C,D,E lower than PHED standards (e.g., most of PHED is at grades A,B,C).
- Grade C,D,E data frequently may have QA/QC problems including lack of field fortification, laboratory recoveries, and/or storage stability information.
- Grade C,D,E data have an insufficient amount of replicates.
- Grade C,D,E data may have higher variabilities (e.g., high CVs).

The following deficiencies of PHED and the residential SOPs should also be noted:

- Data includes all pesticides, not just antimicrobial chemicals, so the results reported in PHED may be misleading.
- Pesticides are not usually volatile, so inhalation unit exposures may be underestimated for antimicrobial chemicals that are volatile.

- The job functions that commonly uses pesticides may be different from those job functions using antimicrobial chemicals.

- The basic assumption underlying the database is that exposure to pesticide handlers is primarily a function of the physical parameters associated with handling and applying rather than the chemical properties of the individual active ingredients.

Other uncertainties regarding exposure estimates are provide below.

- Exposure estimates are performed using traditional EPA/OPP/AD assumptions for amount treated per day (see MBT RED). Specific industry or EPA estimates were not available.

Table 5-7: Toxicology Data Gaps Identified in the Risk Assessment Associated *1,4-Bis(bromoacetoxy)-2-butene* (BBAB)

Data Gaps	Used in Oil Field Injection Water	Used in Water-Based Coatings	Used in Pulp and Paper Mills
Dermal penetration study or 90-day dermal study	**R** [a]	**R** [a]	**R** [a]
28-day inhalation study		**R** [a]	
Neurotoxicity screening battery	**R** [a]	**R** [a]	**R** [a]
Developmental toxicity study in the rabbit			**R** [a,b]
Two-generation reproductive toxicity			**R** [a]
Chronic toxicity study in non-rodents			**R** [a,b]
Carcinogenicity study in the mouse			**R** [a,b]
Combined chronic toxicity/carcinogenicity study in rat			**R** [a,b]
90-day non-rodent toxicity study (with neurotoxicity endpoints)			**R** [a]

Note: (a). R = Required study.
(b). It is not required, if registrant can provide data that show **BBAB** residues in food are less than 200ppb.

5.8 REFERENCES

1. Dietary Exposure Evaluation Model (DEEM™).1998. Novigen Sciences, Inc. N.W.